Notice of Allowability.	Application No.	Applicant(s)	
	10/663,589	HEILMAN ET AL.	
	Examiner	Art Unit	
	Jeffrey Stucker	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *1-24*.

3. ☒ The drawings filed on *16 September 2003* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 16 September 2003
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Bud Nelson on 10 March 2005.

Amendments to the Specification

On page 3, line 18 to page 4, line 8, please replace the paragraph beginning "Polyols, particularly polyethylene glycol.." with the following paragraph:

Polyols, particularly polyethylene glycol (PEG), have been found to be well tolerated and are believed to have a relatively low level of toxicity when used as a pharmaceutically acceptable carrier in an injectable solution of a drug formulation. Thus, PEG has been used as a pharmaceutically acceptable carrier in a number of regulatory-approved injectable solution formulations that contain drug comprising chemical compositions other than peptides and proteins. The amount of PEG in such a formulation is typically present in an amount from about 0.1 weight percent to about 5 weight percent of the formulation. PEG has not been used as a pharmaceutically acceptable carrier for maintaining proteins and peptides in solution, but rather has been used in the precipitation of proteins and peptides. For example, hepatitis B surface antigen protein may be purified using a cycle of precipitation with from 1% to 10% PEG (w/v; see, e.g., U.S. Patent No. 5462863); secretory IgA can be precipitated with PEG at a concentration of 15 to 25 weight per volume (w/v) percent of PEG; fibrinogen can be precipitated with PEG amounting to 2.5% by weight; asparaginase can be precipitated with a solution of 40 to 60 weight percent PEG, and anti-hemophilic factor may be precipitated at a final concentration of 3 percent to 6 percent PEG (w/v). Thus, one concern in using PEG at concentrations equal to or greater than 5 weight percent in a pharmaceutical composition as a ~~pharmaceutcially~~ pharmaceutically acceptable carrier is precipitation out of

solution of the protein or peptide that is to be administered in an injectable solution formulation, a very undesirable effect. In one instance (see, e.g., U.S. Patent No. 6,004,549), disclosed is a pharmaceutical composition comprised of a suspension of a protein in a polyol; i.e., a crystalline form of interferon suspended in a solution or gel containing 40% aqueous solution of PEG8000 (w/v) or a 50% solution of PEG 3350 (the number following "PEG" is approximate molecular size in daltons of the PEG referenced, as will be discussed in more detail herein).

On page 6, lines 2 to 6, please replace the FIG.1 description with the following:

FIG. 1 is a schematic of HIV gp41 showing the heptad repeat 1 region (HR1) and heptad repeat 2 region (HR2) along with other functional regions of gp41. Exemplary peptide sequences corresponding to HIV-1 strain ~~LAI~~ IIIB HR1 (SEQ ID NO:1) and HR2 (SEQ ID NO:2) are shown for purposes of illustration. The amino acid residues are numbered according to their position in gp160, strain $HIV_{\sim\sim LAI\sim\sim IIIB}$.

On page 6, line 15 to page 7, line 1, please replace the paragraph beginning "The term "pharmaceutically acceptable carrier",..." with the following paragraph:

The term "pharmaceutically acceptable carrier", when used herein for purposes of the specification and claims, means a carrier medium that does not significantly alter the biological activity of the active ingredient (e.g., a synthetic peptide comprising an HIV-fusion ~~inihibitor~~ inhibitor) to which it is

added. In accordance with the present invention, a polyol is a pharmaceutically acceptable carrier in the pharmaceutical composition comprising an injectable ~~aqueous~~ aqueous formulation according to the present invention. The pharmaceutical composition may comprise one or more additional pharmaceutically acceptable carriers other than polyol contained therein (i.e., one or more pharmaceutically acceptable carriers in addition to the polyol). As known to those skilled in the art, and for use in an injectable solution or aqueous formulation, a suitable pharmaceutically acceptable carrier may comprise one or substances, including but not limited to, water, buffered water, saline, 0.3% glycine, aqueous alcohols, isotonic aqueous buffer; and may further include one or more substances such as glycerol, oils, salts such as sodium, potassium, magnesium and ammonium, phosphonates, carbonate esters, fatty acids, saccharides (e.g., mannitol), polysaccharides, excipients, and preservatives and/or stabilizers (to increase shelf-life or as necessary and suitable for manufacture and distribution of the composition). Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous or parenteral administration (e.g., by injection).

On page 8, line 33 to page 10, line 27, please replace the paragraph beginning "The terms "synthetic peptide" and..." with the following paragraph:

The terms "synthetic peptide" and "HIV fusion inhibitor" are used synonymously herein, in relation to a peptide employed in the present invention, and for the purposes of the specification

and claims, to mean a peptide (a) produced by chemical synthesis, recombinant expression, biochemical or enzymatic fragmentation of a larger molecule, chemical cleavage of larger molecule, a combination of the foregoing or, in general, made by any other method in the art, and isolated; (b) comprising an amino acid sequence of no less than about 15 amino acids and no more than about 60 amino acid residues in length, and comprises of at least 10 contiguous amino acids contained in either the HR1 region or HR2 region of gp41 of HIV (more preferably of HIV-1); and (c) capable of inhibiting transmission of HIV to a target cell (preferably, by complexing to an HR region of HIV-1 gp41 and inhibiting fusion between HIV-1 and a target cell), as can be determined by assessing antiviral activity *in vitro* and/or *in vivo*, as will be described in more detail herein. The term "isolated" when used in reference to a peptide, means that the synthetic peptide is substantially free of components which have not become part of the integral structure of the peptide itself; e.g., such as substantially free of cellular material or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized or produced using biochemical or chemical processes. The synthetic peptide may comprise, in it's amino acid sequence, one or more conservative substitutions and/or one or polymorphisms found in the sequence of the relevant region of the HIV gp41, or may comprise one or more amino acid substitutions which are added to stabilize helix structure and/or affect oligomerization so that the peptide self-assembles into a trimer (see, for example, the disclosure of co-pending U.S. application number 10/664,021 which is herein incorporated by reference); provided that it retains

antiviral activity against HIV-1. Further, the amino acid sequence, in addition to having a core peptide derived from HIV gp41, may comprise one or more ~~enhacers~~ enhancer peptides linked to the core peptide, e.g., at the N-terminus, at the C-terminus or at both the N-terminus and C-terminus, or may have a core peptide derived from one or more of HIV-1, HIV-2, and SIV (see, e.g., U.S. Patent No. 6,258,782, the disclosure of which is herein incorporated by reference). Depending on the synthetic peptide employed in the pharmaceutical composition, the synthetic peptide may exist as a monomer, or an oligomeric form which may include, but is not limited to, a dimer, trimer, tetramer, or hexamer. For example, ~~as described in more detail in U.S. application number _____,~~ synthetic peptides comprising modified HR1 peptides preferably self-assemble into trimers (e.g., a trimer being comprised of three molecules of synthetic peptide). Preferably, the synthetic peptide employed in the present invention may comprise a sequence of no less than about 15 amino acids and no more than about 60 amino acid residues in length, and preferably no less than 36 amino acids and no more than about 51 amino acids in length, and more preferably no less than about 41 amino acids and no more than about 51 amino acids in length. Preferably, for a synthetic peptide comprising sequence derived from the HR1 region of HIV-1 gp41, the synthetic peptide comprises a contiguous sequence of at least 15 amino acid residues in the amino acid sequence of SEQ ID NO:1, as key determinants in this portion of the HR1 region (e.g., such as, noted by single letter amino acid designation, NNLLRAIEAQQHLL QLTVWGIKQLQARI LAVERYLKD which is amino acid residue 18 to amino acid residue 54 of SEQ ID NO:1) have been found to influence structure, and biochemical and

antiviral parameters described herein. Preferably, for a synthetic peptide sequence derived from the HR2 region of HIV gp41, the synthetic peptide comprises a contiguous sequence of at least 15 amino acid residues in the amino acid sequence of SEQ ID NO:2, and more preferably QQEKNEQEL (which is amino acid residue 43 to amino acid residue 51 of SEQ ID NO:2) as key determinants in this portion of the HR2 region have been found to influence structure, and biochemical and antiviral parameters described herein. Numerous of such synthetic peptides that may be applied to the present invention have been disclosed previously in, for example, U.S. Patent Nos. 5,656,480, 6,133,418, and 6,258,782~~, and U.S. application number~~ _____ (the disclosures of which are herein incorporated by reference in their entirety). For purposes of illustration, exemplary synthetic peptides that may be applied to the present invention include, but are not limited to, synthetic peptides comprising the amino acid sequence listed in SEQ ID NOs: 3-95. "Synthetic peptide" when used herein with "polyol" or "PEG", with respect to being constituents (e.g., each as dissolved solids) in the pharmaceutical composition according to the present invention and for the purposes of the specification and claims, means that the synthetic peptide and polymer are not conjugated together (e.g., are not covalently bonded together).

On page 11, line 12, please replace the paragraph beginning "In this example, illustrated is" with the following paragraph:

In this example, illustrated is a pharmaceutical composition according to the present invention, wherein several embodiments illustrated in this example employ T1249 (SEQ ID NO:5, see U.S. Patent No. 6,258,752). However, it is understood

(and shown by example herein) that synthetic peptide other than T1249 (SEQ ID NO:5) may be employed in the pharmaceutical composition according to the present invention, particularly because this class of synthetic peptides (HIV fusion inhibitor peptides) shares structural, biochemical, and functional features. More particularly, this class of synthetic peptides all comprise coiled coil heptad repeats which may contribute to the molecular interactions of solubility in an aqueous solution containing polyol as described herein in more detail. Other shared structural, biochemical and functional features include, but may not be limited to, an amino acid sequence containing one or more leucine zipper-like motifs, a propensity for ~~coiled~~ coiled coil structure, a propensity for oligomerization, and ability to inhibit transmission of HIV to a target cell.

On page 14, please replace Table 3 with the following table:

Table 3

	X	Y	Z	H	I	J
T-1249 (SEQ ID NO:5) (mg/ml)	100	100	100	200	200	200
PEG 1500 (mg/ml)	92	91.7	91.7	167	167	167
Mannitol (mg/ml)	23.	22.9	22.9	---	---	---
~~PH~~ pH	6.5-9.0	6.8	8.0	6.8-9.0	6.8	8.0

On page 19, line 12 to page 20, line 14, please replace the paragraph beginning "The present invention provides for..." with the following paragraph:

The present invention provides for pharmaceutical compositions which comprises synthetic peptide comprising HIV fusion inhibitors having antiviral activity as evidenced by the ability

to inhibit transmission of HIV to a target cell, and/or to inhibit gp41-mediated fusion of HIV to a target cell. Also provided is a method for treating HIV-1 infection comprising administering to an HIV-1-infected individual a pharmaceutical composition according to the present invention. Preferably, the pharmaceutical composition is in an amount effective to inhibit transmission of HIV to a target cell, and/or in an amount effective to inhibit gp41-mediated fusion of HIV to a target cell.

The method may ~~comprises~~ comprise contacting the virus, in the presence of the cell, with a concentration of a pharmaceutical composition according to the present invention effective to inhibit infection of the cell by HIV. Also, the method may comprise adding to the virus and the cell an amount of a pharmaceutical composition according to the present invention effective to inhibit gp41-mediated fusion between the virus and the cell. These methods may be used to treat HIV-infected individuals (therapeutically) or to treat individuals newly exposed to or at high risk of exposure (e.g., through drug usage or high risk sexual behavior) to HIV (prophylactically). Thus, for example, in the case of an HIV-1 infected individual, an effective amount of the pharmaceutical composition would be a dose sufficient (by itself and/or in conjunction with a regimen of doses) to reduce HIV viral load in the individual being treated. As known to those skilled in the art, there are several standard methods for measuring HIV viral load which include, but are not limited to, by quantitative cultures of peripheral blood mononuclear cells and by plasma HIV RNA measurements. In a method according to the present invention, the pharmaceutical composition of the invention can be

administered in a single administration, intermittently, periodically, or continuously, as can be determined by a medical practitioner, such as by monitoring viral load. A pharmaceutical composition according to the present invention may show synergistic results, of inhibiting transmission of HIV to a target cell, when used in combination (e.g., when used simultaneously, or in a cycling on with one drug and cycling off with another) with other antiviral drugs used for treatment of HIV (e.g., including, but not limited to, other HIV entry inhibitors (e.g., CCR5 inhibitors, retrocyclin, and the like), HIV integrase inhibitors, reverse transcriptase inhibitors (e.g., nucleoside or nonnucleoside), protease inhibitors, and the like, as well known in the art) (see, e.g., U.S. Patent No. 6,475,491, the disclosure of which is herein incorporated by reference).

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (currently amended) A pharmaceutical composition comprised of an aqueous solution comprising synthetic peptide in admixture with a polyol; wherein the synthetic peptide is an HIV fusion inhibitor; wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 70 mg/ml and not more than 500 mg/ml; and wherein the polyol is in a final concentration of no less than 5 weight % and no more than 75 weight % of the pharmaceutical composition.

2. (previously presented) The pharmaceutical composition according to claim 1, wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml.

3. (previously presented) The pharmaceutical composition according to claim 1, wherein the polyol is in a final concentration of no less than 10 weight % and no more than 50 weight % of the pharmaceutical composition.

4. (previously presented) The pharmaceutical composition according to claim 1, wherein the polyol comprises polyethylene glycol.

5. (previously presented) The pharmaceutical composition according to claim 1, further comprising a pharmaceutically

acceptable carrier additional to the polyol.

6. (currently amended) A method of treating HIV infection ~~(preferably, HIV-1 infection)~~ comprising administering to an HIV-infected individual a pharmaceutical composition according to claim 1.

7. (currently amended) A pharmaceutical composition comprised of an aqueous solution comprising synthetic peptide in admixture with a polyol; wherein the synthetic peptide is an HIV fusion inhibitor; wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml; and wherein the polyol is in a final concentration of no less than 10 weight % and no more than 50 weight % of the pharmaceutical composition.

8. (previously presented) The pharmaceutical composition according to claim 7, wherein the polyol comprises polyethylene glycol.

9. (previously presented) The pharmaceutical composition according to claim 7, further comprising a pharmaceutically acceptable carrier additional to the polyol.

10. (currently amended) A method of treating HIV infection ~~(preferably, HIV-1 infection)~~ comprising administering to an HIV-infected individual a pharmaceutical composition according to claim 7.

11. (currently amended) A synthetic peptide-containing

pharmaceutical composition as a unit dose, wherein the pharmaceutical composition comprises an aqueous ~~formulation~~ solution comprising: (a) a polyol present as a pharmaceutically acceptable carrier in an amount not less than 5 weight % and not more than 75 weight % of the pharmaceutical composition as a unit dose; and (b) synthetic peptide comprising an HIV fusion inhibitor in a final concentration of the pharmaceutical composition of not less than 70 mg/ml and not more than 500 mg/ml.

12. (previously presented) The synthetic peptide-containing pharmaceutical composition according to claim 11, wherein the synthetic peptide is in a final concentration in the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml.

13. (previously presented) The synthetic peptide-containing pharmaceutical composition according to claim 11, wherein the polyol is in a final concentration of no less than 10 weight % and no more than 50 weight % of the pharmaceutical composition.

14. (previously presented) The synthetic peptide-containing pharmaceutical composition according to claim 11, wherein the polyol comprises polyethylene glycol.

15. (previously presented) The synthetic peptide-containing pharmaceutical composition according to claim 11, further comprising a pharmaceutically acceptable carrier additional to the polyol.

16. (currently amended) A method of treating HIV infection ~~(preferably, HIV-1 infection)~~ comprising administering to an HIV-infected individual a synthetic peptide-containing pharmaceutical composition according to claim 11.

17. (currently amended) A synthetic peptide-containing pharmaceutical composition as a unit dose, wherein the pharmaceutical composition comprises an aqueous ~~formulation~~ solution comprising: (a) a polyol present as a pharmaceutically acceptable carrier in an amount not less than 10 weight % and not more than 50% of the pharmaceutical composition as a unit dose; and (b) synthetic peptide comprising an HIV fusion inhibitor in a final concentration of the pharmaceutical composition of not less than 100 mg/ml and not more than 250 mg/ml.

18. (previously presented) The synthetic peptide-containing pharmaceutical composition according to claim 17, wherein the polyol comprises polyethylene glycol.

19. (previously presented) The synthetic peptide-containing pharmaceutical composition according to claim 17, further comprising a pharmaceutically acceptable carrier additional to the polyol.

20. (currently amended) A method of treating HIV infection ~~(preferably, HIV-1 infection)~~ comprising administering to an HIV-infected individual a synthetic peptide-containing pharmaceutical composition according to claim 17.

21. (new) A method of treating HIV infection comprising administering to an HIV-infected individual a pharmaceutical composition according to claim 5.

22. (new) A method of treating HIV infection comprising administering to an HIV-infected individual a pharmaceutical composition according to claim 9.

23. (new) A method of treating HIV infection comprising administering to an HIV-infected individual a synthetic peptide-containing pharmaceutical composition according to claim 15.

24. (new) A method of treating HIV infection comprising administering to an HIV-infected individual a synthetic peptide-containing pharmaceutical composition according to claim 19.

The following is an Examiner's Statement of Reasons for Allowance:

The claimed invention is composition comprised of an aqueous solution comprising a peptide in admixture with a polyol wherein the peptide is an HIV fusion inhibitor and methods of treating HIV infection with the composition. The composition is an aqueous solution of a polyol as described at the bottom of page 10 to the top of page 11 of the instant specification which is a solution as distinct from a suspension. The peptide and polyol are in an admixture, not bonded together which is defined on page 10, lines 25-28.

Bolognesi et al. (5,464,933) teaches anti-HIV peptides but does not teach or suggest incorporating them into an aqueous solution of polyol.

Coombes et al. teach PEG-DEX conjugates as drug delivery compositions. This reference teaches the polyols as particles which does not read on the instantly claimed aqueous solution.

Cleland et al. (5,589,167) teaches an aqueous solution comprising a polypeptide and a polyol but this does not read on the instant pharmaceutical composition because the '167 composition is an intermediate in the production of the final pharmaceutical composition which is in an organic solvent. There is no suggestion to stop at the intermediate stage.

Chandrashekar et al. (6,143,314) teaches a slow release composition comprising a polymer comprising the polyol PEG which does not read on the instantly claimed invention because this patented composition includes an organic solvent and does not suggest that the organic solvent can be substituted by an aqueous solution.

Harris (US 2004/0076602A1) teaches crosslinked PEG gels and does not teach or suggest that these gels are modifiable to be in solution.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

The Group 1600 Official Fax number is: (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system,

see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Stucker whose telephone number is (571)-272-0911. The examiner can normally be reached Monday to Thursday from 7:00am-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (571)-272-0902.

JEFFREY STUCKER
PRIMARY EXAMINER